Chapter 14

Intratympanic Steroid Treatment in Méniére Disease

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Abstract

Méniére disease (MD) is characterized by vertigo attacks, hearing loss, tinnitus, and aural fullness. Although the exact treatment of MD is lacking, several treatment options including conservative, medical, and surgical aim to control symptoms. Recently, an increasingly used treatment method called intratympanic steroid (ITS) treatment is applied to patients suffering from MD. In which step the ITS takes part for MD treatment protocol is not certain. But common wisdom is that ITS can be used in patients with intractable MD to conservative and medical treatment before applying intratympanic gentamicin and surgical treatments.

Keywords: Méniére Disease, Steroid Treatment, Vertigo

1. Introduction

Méniére disease (MD) is characterized by vertigo attacks, hearing loss, tinnitus, and aural fullness. Several treatment options include conservative, medical, and surgical aims to control symptoms. Recently, an increasingly used treatment method called intratympanic steroid (ITS) treatment is applied to patients suffering from MD. In this chapter, we mention this alternative treatment option.

2. Pathophysiology

After Mc Cabe's report on auto-immune depended on sensorineural hearing loss in 1979, immunological mechanisms about inner ear pathologies started to be investigated [1]. Many

studies showed that MD is an immune system-related disease. Autoantibody for the Raf-1 protein in the membranous labyrinth is found in patients with MD [2]. Elevated IgG immune complexes, auto-immune response to type II collagen, and focal inflammation with intraepithelial invasion caused by mononuclear cells are shown in endolymphatic sac. This phenomenon is also called "endolymphatic sacitis" [3, 4].

Rarey and Curtis found glycocorticoid receptors on the cochlea and vestibule (especially on the spiral ligament) [5]. Lohuis also showed cell atrophy on stria vascularis after adrenal steroid defects [6]. Glycocorticoid receptors are also found in the lateral wall of cochlea, organ of Corti, modiolus, vestibule, and stria vascularis [7].

It is already shown that steroids regulate inner ear fluid balance with potassium transport channels by mineralocorticoid receptor genes and aquaporin regulation [8, 9]. Cochlear blood flow is also positively affected by topical steroid application [10, 11].

According to these information and steroids' anti-inflammatory/immunosuppressive effects, we can say that ITS treatment is helpful for MD control.

3. Intratympanic steroid injection protocol

Procedure is done under operation microscope. Head is turned 45° to the opposite side. EMLA® 5% cream (lidocaine Hcl + prilocaine) or 88% phenol can be used for local anesthesia. Twenty-two or 25 gauge spinal needle can be used for injection. Myringotomy is made anterosuperior part of tympanic membrane to fill middle ear as long as possible. After intervention, the patient has to wait for 30–40 min as the head is turned 45° to the opposite side. During this time, the patient is requested not to speak and not to swallow as much as possible [12, 13].

4. Application features (steroid types, daily usage time, dosage, and time duration)

Despite many studies, there is no consensus for ITS application [14]. Three different types of steroids are used for ITS: hydrocortisone (short-acting), methylprednisolone (intermediate-acting), and dexamethasone (long-acting). Methylprednisolone and dexamethasone are generally preferred types in studies (**Table 1**). In some studies, it is claimed that methylprednisolone reaches inner ear tissues and fluids in shorter time (2 h), and maximum concentration continues by 6 h [4, 15]. However, other studies have claimed that dexamethasone reaches inner ear tissues and fluids in shorter time than methylprednisolone [15, 16].

Three different application ways are used for ITS: injection, ventilation tube, and perfusion with catheter. Daily intervention is recommended regardless of application ways. Methylprednisolone stays for 6 h at maximal concentration in blood and descends as basal level at 24 h. Dexamethasone also descends as basal level at 6 h. We recommend using a ventilation

Types of ITS in MD	Hydrocortisone	Methylprednisolone*	Dexamethasone*
Efficiency period	**Short-acting**	**Intermediate-acting**	**Long-acting**
Dosage		62.5 mg/ml, 3 weeks [3]	4 mg/ml, three times with 3 days interval [14, 18]
			17.5 mg, 0.3–0.8 ml applied each day for 5 days [12]
			4 mg/cc, 4 weeks [13]
			24 mg/cc [20]
			0.20 mg/cc, five drops in each day for 3 months [19]

*Preferred steroid types in studies, ITS: intratympanic steroid, MD: Méniére disease.

Table 1. Types, efficiency period, and dosage of ITS using in MD.

tube or catheter application for daily intervention that provides less patient pain and prevents time lost for both doctor and patient [15, 17].

Both the dosing of the steroid types and the daily usage protocols are also different in the studies. Dexamethasone (4 mg/ml) is used for three times at 3 days interval in two studies [14, 18]. In another study, 17.5 mg dexamethasone in 0.3–0.8 ml was applied each day for 5 days [12]. Ventilation tube application was made toward posteroinferior cadrane to 20 patients with MD in another study. In that study, 1 mg/cc dexamethasone was distilled to 0.20 mg/cc with water. Five drops were applied to 20 patients in each day for 3 months (**Table 1**) [19]. Barr et al. administered 4 mg/cc dexamethasone for 4 weeks [13]. Hamid et al. applied 24 mg/cc dexamethasone (**Table 1**) [20]. Nathalie Gabra et al. used methylprednisolone (62.5 mg/ml) each week for 3 weeks (**Table 1**) [3]. The reason for not performing daily intervention in these studies is the difficulty of injection application way [14]. All studies mentioned earlier show that vertigo control rates get higher when drug concentration increases.

5. Advantages

Steroids are permeable to round window and across blood-labyrinthine barrier [13] so drug concentration in inner ear fluids (both perilymph and endolymph) is higher with ITS application than systemic administration [3, 13]. ITS application also prevents steroid side effects.

6. Disadvantages and side effects

Tympanic membrane perforation may occur after ITS. Its incidence seems low and changes between 0 and 5.1%. If the tympanic membrane perforation develops after ITS, it may recover or be permanent [12, 14, 18, 21]. To reduce the likelihood of development perforation, it needs attention to not penetrate tympanic membrane from thinned areas.

Pain and burn sensation in the ear and pharynx are other problems. These resolve approximately 0.5–1 h later. Mild dizziness and transient vertigo may be seen due to inner ear content concentration change [4, 13, 18].

7. Treatment effects

Patients with MD suffer from vertigo attacks, hearing loss, tinnitus, and aural fullness. Life is also unbearable during MD attacks. We mention each symptom recovering rate by ITS treatment in subsequent text (**Table 2**).

	Vertigo	Hearing loss	Tinnitus	Aural fullness	Quality of life
Albu et al. [14]	46% class A 21.2% class B 24.2% class C/D 3% class E	PTA: Pretreatment 57.4 ± 14.7 After 1 year 55.8 ± 15.5	THI: Pretreatment 28.6 ± 14.3 Posttreatment 23.5 ± 12.4	–	DHI: Pretreatment 53.2 ± 13.4 Posttreatment 40.7 ± 16.5
Casani et al. [18]	42.9% class A 17.9% class B 32.2% class C/D 7% class E/F	PTA: Pretreatment 66.6 ± 16.4 After 1 month 67.5 ± 17.7 After 1 year 67.1 ± 17.6 After 2 years 65.0 ± 18.7	–	–	–
Gabra and Saliba [3]	**Number of attack** Before therapy: 5.3 ± 6.41 After 0–6 months: therapy 1.4 ± 1.87 After 6–12 months: therapy 1.4 ± 1.87	PTA: Pretreatment 41.89 ± 14.92 After 1 yeary 49.51 ± 17.9	Decreased to: 78% at 0–6 months therapy 68% at 6–12 months therapy	Pretreatment: 95.2% Posttreatment: 65%	–
Paragache et al. [19]	85% class A 10% class C/D 5% class E/F	PTA:15% improved 10% dropped SDS:15% improved 85% same	10% recovery 60% improved	15% Disappeared 65% Improved	–
Ren et al. [12]	48.8% class A 20.9% class B 9.3% class C/D 20.9% class E	–	Disappeared 11.6% Decreased 48.8% Same 23.3% Improved 16.3%	16.7%: Disappeared 45.8%: Alleviated 35.7%: Intensive	–
Barr et al. [13]	At 3rd month of therapy: 52% class A At 6th month of therapy: 43% class A	At 6th month of therapy: An average loss of 2.7 dB	–	–	–

	Vertigo	Hearing loss	Tinnitus	Aural fullness	Quality of life
Garduño-Anaya et al. [22]	82% class A 18% class B	PTA: Pretreatment 55.7 After 2 years 53.4 SDS: Pretreatment 68.5% After 2 years 66.7%	THI: 61 pretreatment 22.3 at 2 years therapy GTS: 3.2 pretreatment 1.6 at 2 years therapy	48% subjective improvement	DHI: Pretreatment 68.7 Posttreatment 8.3

ITS: Intratympanic steroid, MD: Méniére disease, PTA: Pure tone average, SDS: Speech discrimination score, THI: Tinnitus Handicap Inventory, GTS: Grading of Tinnitus Severity, DHI: Dizziness Handicap Inventory.

Table 2. Symptom relief success of ITS on MD.

7.1. Vertigo

Vertigo control is generally reported according to the 1995 AAO-HNS guidelines or Sakata's criteria in the studies about ITS treatment.

Albu et al. investigated 66 patients with definite unilateral MD. Thirty-three of them received IT dexamethasone. Fourteen patients (46.6%) were free from vertigo attack (class A), seven patients (21.2%) had substantial control (class B), and eight patients (24.2%) had limited control (classes C and D) at 1-year follow-up. Vertigo control couldn't be obtained in one patient (class E). Failures were planned for intratympanic gentamicin (ITG), which did not benefit enough from the ITC [14].

In Casani et al.'s study, 12 patients (42.9%) had full vertigo control (class A), 5 patients (17.9%) had substantial control (class B), 9 patients (32.2%) had limited control (class C or D) despite 1 or 2 additional intratympanic dexamethasone (ITD). Two patients (7%) couldn't get vertigo control (class E or F) and were scheduled for ITG therapy [18].

In a study, Gabra and Saliba had evaluated the effect of intratympanic methylprednisolone and gentamicin injection on MD. In this study, the number of patient's vertigo attacks per month before ITS (for methylprednisolone) was 5.3 ± 6.41 (n = 42). In 0–6 months after the ITS, the number of attacks decreased to 2.3 ± 3.20 (n = 41). Finally, 6–12 months after ITS, attack frequency was 1.4 ± 1.87 (n = 27). In the first period after treatment, 41.5% of the patients achieved complete control of vertigo. In the second period after treatment, 48.1% of the patients achieved complete control of vertigo (P = 0.004). There was a statistically significant decrease in the number of vertigo attacks in the first period (P = 0.025) and no difference between the 0- to 6-month and 6- to 12-month periods after ITS (P = 0.95) [3].

Paragache et al. reported 85% (17 of 20 patients) control of vertigo with intratympanic dexamethasone therapy. Two patients (10%) had only limited control. One patient (5%) had worsening of vertigo during treatment [19].

Boleas-Aguirre et al. reported 91% "acceptable" vertigo control using 12 mg/ml dexamethasone. Most of the patients (63%) needed more than one series of treatment for achieving remission of MD [21].

Ren et al. reported complete control of vertigo in 21 of 43 patients (48.8%), substantial control in 9 patents (20.9%), limited control in 4 patients (9.3%), and no exact response in 9 patients (20.9%) with intratympanic dexamethasone injections for refractory MD after 18 months follow-up [12].

In a retrospective analysis of 17 intractable MD patients treated with ITD, short-term (after 6 months) and long-term (after 24 months) vertigo control rates were 94 and 81% [4].

Barrs's et al. reported that 21 patients with intractable MD underwent intratympanic injections of 4 mg/ml dexamethasone over a period of 4 weeks as an office procedure. Eleven (52%) of 21 patients were free for vertigo attack at the 3rd month of treatment. However, vertigo attacks relapsed in two patients and success rate decreased to 43% at the 6th month. At 1-year follow-up, six of remaining nine patients had no vertigo attack. Recurrent injections applied to five patients who responded at the beginning but repeated vertigo attacks later. Vertigo was controlled in three of those five patients. One patient got only one additional injection but two patients got multiple injections for each month up to 6 months [13].

In another prospective, randomized, double-blind study with a 2-year follow-up, the effect of five consecutive daily intratympanic injections of dexamethasone on 22 patients having definite MD was investigated. Complete control of vertigo (class A) was achieved in 9 of 11 patients (82%) and substantial control of vertigo (class B) in the remaining 2 patients (18%) [22].

In a retrospective study including 129 patients diagnosed with unilateral MD still having vertigo despite medical therapy, patient's satisfaction with vertigo attack control using ITD (12 mg/ml) was assessed. Vertigo control was obtained in 117 (91%) of 129 patients. One injection was enough for 48 patients (37%), two injections were needed for 26 patients (20%), three injections for 18 patients (14%), and four injections for 10 patients (8%). More than four injections were needed for 15 patients (21%). Ninety-six patients were followed for 2 years. Vertigo control was obtained in 87 (91%) patients with ITD. After 2 years, additional injection wasn't needed in 61 patients but repeated injections were required in 23 patients. Three patients requested ITG treatment because of repeated ITD injections [21].

Different vertigo control rates were given in studies mentioned earlier. This may be related to steroid type, concentration, time duration, and frequency of therapy. Also keep in mind that each drug has different personal effect.

7.2. Hearing loss

Sensorineural hearing loss is another symptom of MD. It may be transient or permanent. The success of any treatment about MD on hearing improvement is a change of 10 dB or more in pure tone average (PTA) or a change of 15% in speech discrimination score (SDS) according to 1995 AAO-HNS guidelines [3, 14, 18].

Paragache et al. observed hearing improvement in only three patients (15%) with two patients (10%) having a 20-dB improvement in threshold and one patient (5%) having a 10-dB

improvement in threshold. In 10% of patients, the hearing level was observed to decrease. The speech discrimination score improved in three patients (15%). For the rest, the SDS remained the same with the intratympanic dexamethasone applications [19].

Albu et al. found the mean pretreatment PTA as 57.4 (standard deviation (SD), 14.7) with the intratympanic dexamethasone injection. After 12 months of therapy, the PTA values were 55.8 (SD, 15.5). Hearing was unchanged in 14 patients, improved in 4 patients and worsened in 12 patients. With reference to hearing outcomes, they had demonstrated that hearing conservation was only able to be maintained in patients reporting vertigo, which was well controlled. As previously stated [18], hearing loss is associated with the evolution of MD [14, 23].

Casani et al. found the mean pretreatment PTA as 66.6 (SD, 16.4). After 1 month with ITD injection, the PTA values changed on average to 67.5 (SD, 17.7). The mean PTA was 67.1 (SD, 17.6) at 1 year and 65.0 (SD, 18.7) at 2-year follow-up with the intratympanic ITD injection. No significant variations of SDS were observed during each follow-up period ($P > 0.05$) [18]. Hearing improved in 3 patients (10.7%) and did not worsen in 13 patients (46.4%). Vertigo was detected as class A and class B in those 16 patients. Hearing deterioration on PTA was more than 10 dB in remaining 10 patients who couldn't obtain vertigo control [18]. It pays attention that a correlation was found between hearing deterioration and vertigo attack persistence.

Gabra et al. found the mean PTA as 41.89 ± 14.92 dB before intratympanic methylprednisolone injection (ITM). There was a slight increase in PTA at 6 months. This was followed by an increase in PTA at 12 months after ITM, the mean PTA was 49.51 ± 17.9 dB. There was no statistically significant difference in the evolution from before to after treatment ($P = 0.456$ for the 0- to 6-month period and $P = 0.06$ for the 6- to 12-month period) [3]. In the first 0–6 months, the SDS decreased and remained stable in the second period. There was no statistically significant difference in the evolution of SDS after ITM [3].

Another retrospective analysis was conducted on 17 MD patients treated with ITM. Sixteen patients were followed up for more than 2 years. The PTA was 53 ± 14 dB before treatment, and 50 ± 16 dB at 6 months and 52 ± 20 dB at 24 months after ITM. Thus, a significant improvement in PTA after 6 months had returned to the pretreatment baseline after 2 years and there were no significant differences in clinical stage, based on hearing changes at the 6- and 24-month follow-up [4].

Garduño-Anaya et al. found the mean initial PTA as 55.7 dB and after receiving the ITD the mean PTA was 53.4 dB at 2-year follow-up. Only one patient's hearing (9%) improvement, 10 dB or more according to the 1995 AAO-HNS criteria, was considered to be clinically significant. One of 11 patients was demonstrated to have hearing deterioration of 10 dB at 2-year follow-up [22]. The mean SDS was 68.5% at the beginning of treatment and 66.7% after 2 years of ITD. According to 1995 AAO-HNS criteria, 15% or higher improvement on SDS was provided in two patients (18%). Only one (9%) of 11 patients got 15% or higher deterioration at 2 years follow-up. They reported a subjective improvement of 35% in hearing loss [22].

Kaplan et al. investigated 30 patients (20 women and 10 men, aged 28–85 years) with MD who underwent intratympanic dexamethasone perfusion. Six patients obtained 10 dB or higher improvement at PTA and six patients obtained 15% or higher improvement at SDS at short-term period (4 weeks after perfusion). Those patient numbers decreased to 5 and 2 at 12 months later, respectively [23].

Arriaga and Goldman demonstrated that only 33% of patients had hearing improvement, and 20% of patients had hearing deterioration after ITD with hyaluronan. However, Hillman et al. [24] reported 40% of patients who had hearing improvement after ITD [21].

7.3. Tinnitus

In Paragache et al.'s study, 2 patients (of 20, 10%) showed complete relief from tinnitus and tinnitus improved in 12 patients (60%) [19]. In Gabra et al.'s study, all patients suffered from tinnitus before ITM injections. Tinnitus rate decreased to 78% for 0–6 month period and 68% for 6–12 months period [3]. Tinnitus symptom disappeared in 5 (11.6%) of 43 patients, decreased in 21 (48.8%) patients, didn't change in 10 (23.3%) patients, and increased in 7 (16.3%) patients after ITD in Ren et al.'s study [12].

In a retrospective analysis of 17 intractable MD patients treated with ITM perfusion, 16 patients were followed up for more than 2 years. Tinnitus was controlled in three patients and improved in two patients at the 24-month follow-up, and patient without tinnitus worsened over this interval [4].

Another study measured tinnitus severity with "Tinnitus Handicap Inventory" score and the "Grading of Tinnitus Severity." Eleven patients with unilateral MD were treated with ITD. The initial mean handicap score was 61 and after receiving ITD was 22.3 at 2 years of follow-up. At 2 years of follow-up, a handicap score of 0 was found in 4 of 11 patients (36%) [22]. The initial "Grading of Tinnitus Severity" score was 3.2 and after receiving ITD injection was 1.6 at 2 years of follow-up. Grade 1 of the Grading of Tinnitus Severity (THI 0–16) at 2-year follow-up was achieved by 8 of 11 patients (72%). At 2-year follow-up, 1 of 11 patients (9%) in the dexamethasone group reported improvement of 100% and 1 other patient (9%) reported 90% improvement. Five of 11 patients (45%) reported 0% improvement. The mean subjective improvement at 2-year follow up was 48.1% [22].

7.4. Aural fullness

Garduno-Anaya et al. pointed out a 48% subjective improvement in aural fullness with ITD [21]. In Ren et al.'s study, aural fullness was complained in 24 of 43 patients. It was disappeared in 4 of 24 patients (16.7%), alleviated in 11 patients (45.8%), and even intensive in 9 patients (37.5%) after ITD injection [12].

Another study included 20 patients with MD; aural fullness was completely resolved in 3 patients (15%) and showed some improvement in 13 patients (65%) after ITD application from ventilation tube by the end of 6 months [19]. In other study including 42 patients treated with ITM, 95.2% had aural fullness before ITM and 65% after ITM by the end of 1-year period [3].

7.5. Live functional activity/quality of life

She et al. found improvement in 94% at 6 months and 87% at 24 months on functional activity after ITM perfusion [4].

In Garduño-Anaya et al.'s study, the initial mean "Dizziness Handicap Inventory" score was 68.7. After receiving ITD, the score was 8.3 at 2 years of follow-up [22].

In Kyrodimos et al.'s study, 30 patients (20 women and 10 men, aged 28–85 years) with MD underwent intratympanic 24 mg/ml of dexamethasone perfusion, and were assessed with the assistance of the Glasgow Benefit Inventory (GBI) questionnaire. Follow-up ranged from 12 to 48 months (mean 30 months) with regard to the GBI responses, nine patients (50%) expressed an overall benefit, while six (33%) expressed no benefit and three patients (17%) complained of negative effect after the intervention [25].

Albu et al. investigated 30 patients with intractable unilateral MD. Before therapy, Dizziness Handicap Inventory (DHI) was 53.2 ± 13.4 and after 12 months follow-up, it was 40.7 ± 16.5. Tinnitus Handicap Inventory (THI) was 28.6 ± 14.3 before therapy and 23.5 ± 12.4 after therapy. Both DHI and THI scores were statistically significant with pre- and posttreatment comparison ($P < 0.001$). At 12 months follow-up, level 1 of Functional Level Score (FLS) was attained in 14 (46.7%) patients and level 2 in 9 (30%) patients [14].

8. Comparison with other treatment methods

Although the exact treatment for MD is still not discovered, several treatment options are available. Caffeine, alcohol, theine and salt (CATS) restriction, diuretics, vasodilators, betahistine, intratympanic injection of gentamicin or corticosteroids, and surgery are most accepted treatment strategies [26].

The initial treatment for MD is diet restriction and oral/parenteral medications. Resistance to this therapy, minimal invasive procedures like intratympanic injections are attempted. The last chance to control symptoms is surgery despite complications (**Figure 1**) [13]. In this section, we compare ITS with other treatment options.

First of all, it must be searched whether ITS has a placebo effect or not. Hu et al. disputed the importance of placebo treatment in MD patients [27]. A double-blind randomized crossover trial using ITD (8 mg/ml) showed no benefit over placebo [28].

Hirvonen et al. also used intratympanic and systemic dexamethasone in 17 patients with MD. They claimed that symptoms of aural fullness, hearing loss, tinnitus, and vertigo did not improve significantly and the clinical use of dexamethasone in MD needs further investigation [16].

On the contrary, another randomized placebo controlled trial showed complete control of vertigo attacks in 82% of patients treated with ITD compared with 57% of those receiving placebo [22].

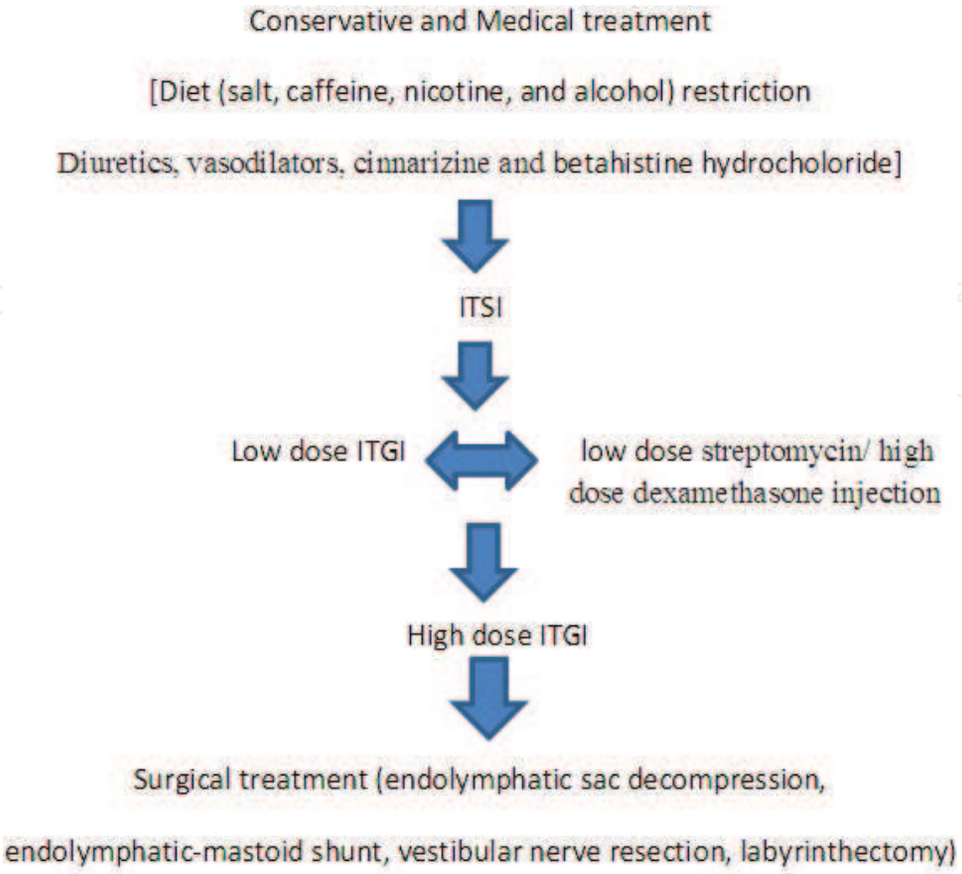

Figure 1. The initial treatment for MD.

Several studies also compare the efficacy of conventional medical treatment and ITS. In Paragache et al.'s study, study group was constituted from 20 patients who was applied ITS and control group was also constituted from 20 patients. Control group patients' diet was free from salt, caffeine, nicotine, and alcohol. Medical management was formed from cinnarizine 25 mg tablets TDS for acute episodes and betahistine hydrochloride 16 mg tablets TDS for continuous treatment. All patients were followed up for 6 months, and results were assessed at 1st, 2nd, 3rd, and 6th months. Vertigo control was 85% at study group and 80% at control group. Hearing loss recovered in three (15%) patients in study group and two (10%) patients in control group. An improvement on SDS was obtained in three (15%) patients in study group and two (10%) patients in control group. Other patients' SDS values were the same. Tinnitus disappeared in two patients in study group and three patients in control group. Tinnitus severity decreased in 12 patients in study group and 10 patients in control group. Aural fullness disappeared in three patients in study group and five patients in control group. Aural fullness severity decreased in 13 patients in study group and 11 patients in control group. They found that both modalities of therapy have almost equal efficacy on MD symptoms, and ITS therapy has an edge over conventional therapy in cases with severe attacks and shorter duration of symptoms [19].

Albu et al. compared the efficacy of ITD and high-dosage betahistine 144 mg/day (48 mg tid). Sixty-six patients with definite unilateral MD were randomly divided in two groups,

each comprising 33 patients: Group A received a combination of ITD and identical appearing placebo pills, while Group B received a combination of high-dosage betahistine and IT saline. Fifty-nine patients completed the study and were available at 12 months for analysis, while seven patients (three in Group A and four in Group B) were excluded because of insufficient compliance. The mean number of vertigo attacks per month was recorded at baseline, at 1, 3, and then every 3 months for up to 1 year. Vertigo control was complete (class A) in 14 (46.6%) patients, partial (class B) in 7 (21.2%) patients, and limited (class C or D) in 8 (24.2%) patients in Group A. Vertigo couldn't be controlled in one (3%) patient (class E) in Group A. Vertigo control was complete (class A) in 12 (36.4%) patients, partial (class B) in 5 (15.2%) patients, and limited (class C or D) in 10 (30.4%) patients in Group B. Vertigo couldn't be controlled in two (6.1%) patients (class E) in Group B. Patients whose vertigo attacks couldn't be controlled in both groups were scheduled for ITG therapy. Vertigo control rate wasn't statistically different between two groups. But vertigo attack frequency was 8.6 in Group A and 7.9 in Group B before treatment. It was 1.8 in Group A and 4.3 in Group B after 1 month of treatment. It became 1.5 for Group A and 2.4 for Group B after 3 months of therapy.

According to those results while ITD has a rapid effect to prevent vertigo attack, betahistine and ITD have similar effect on vertigo attack at the end of 3rd month. [14]. Regarding quality of life, while FLS was found level 1 in 14 patients and level 2 in 9 patients in group A, it was found level 1 in 10 patients and level 2 in 9 patients in group B. There was no statistical significance about FLS for both groups [14]. The mean PTA was 57.4 ± 14.7 dB in Group A and 58.2 ± 13.9 dB in Group B before treatment. It became 55.8 ± 15.5 dB for Group A and 56.1 ± 12.5 dB for Group B after 1-year treatment. There was no statistical significance on hearing level and SDS for both groups. A significant reduction in tinnitus assessed by THI at the end of the follow-up was reported in both treatment groups. The difference among the two groups was not significant [14]. They demonstrated that ITD has an immediate effect while higher dosage of betahistine (144 mg/day) is able to get the same outcome only after 3 months of treatment [14].

Intratympanic gentamicin is a traditional treatment for resistant MD. Despite effective vertigo attack control, ototoxicity is a feared complication. Low-dose ITG protocol was used to overcome this complication in some studies [29–31].

Casani et al. compared the effectiveness of ITG and ITD in a study. In this study, patients were randomized and divided into two groups: 32 patients were treated with ITG and 28 patients were treated with ITD. All measurements were obtained immediately before the treatment and were repeated after 1 month, 1 year, and 2 years following the procedure. Vertigo control was complete (class A) in 26 (81.3%) patients, partial (class B) in four (12.5%) patients, and limited (class D) in one (3.2%) patient in ITG group. Vertigo control couldn't be obtained in one patient and vestibular neurectomy was recommended. Vertigo control was complete (class A) in 12 (42.9%) patients, partial (class B) in 5 (17.9%) patients, limited (class C or D) in 9 (32.1%) patients in ITD group. Vertigo control couldn't be obtained in two patients and they were scheduled for gentamicin treatment. There was no statistical significance for vertigo control in both groups ($P < 0.001$) [18]. Level 1 FLS was obtained in 13 (40.6%) patients in ITG group and 11 (39.3%) patients in ITD group at 1-year follow-up. But level 1 FLS was obtained

in 22 (71%) patients in ITG group and in 12 (46.1%) patients in ITD group at 2-year follow-up. Although there was no statistical significance at 1-year follow-up, significance was found at 2-year follow-up ($P < 0.05$) [18]. The mean PTA was 58.7 ± 13.3 dB in ITG group and 56.5 ± 13.4 dB in ITD group before treatment. It was 61.3 ± 14.6 and 53.7 ± 15.6 dB in ITG and ITD groups, respectively, after 1 month treatment. At first year, it became 62.3 ± 15.3 and 54.6 ± 16 dB, at second year 64.5 ± 15.5 and 56 ± 17.3 dB for both groups, respectively. There was statistical significance on PTA for both groups ($P > 0.05$) [18]. SDS was found to be 67 ± 19 before treatment, 63.1 ± 20 after 1 month treatment, 61.1 ± 21.1 after 1 year treatment, and 60.3 ± 22.6 after 2 year treatment for ITG group. It was found to be 66.6 ± 16.4 before treatment, 67.5 ± 17.7 after 1 month treatment, 67.1 ± 17.6 after 1 year treatment, and 65.0 ± 18.7 after 2 year treatment for ITD group. The only one value for SDS that reached statistical significance was the difference between pretreatment and after 1 month treatment in ITG group ($P < 0.05$). In the ITD group, no significant variations of SDS were observed during each follow-up ($P > 0.05$) [18]. According to 1995 AAO-HNS criteria, hearing got worse in four (12.9%) patients, not changed in 27 (84.4%) patients, and improved in one (3.1%) patient in ITG group after 2-year treatment. Hearing became worse in 12 (42.9%) patients, not changed in 13 (46.4%) patients, and improved in 3 (10.7%) patients in ITD group after 2-year treatment. Vertigo control was classes A and B in 16 patients in ITD group whose hearing didn't get worse [18]. Total or partial vertigo attack control (class A or B) was over 90% for ITG group and 61% for ITD group after 2-year treatment. According to this study, low-dose ITG therapy was more successful than ITD for vertigo attack control [18]. Regarding the hearing outcome, no statistically significant differences were verified between the two groups in terms of mean PTA and SDS values. On the whole, the mean PTA and SDS values were slightly better for the patients treated with ITD [18]. The authors claimed that low-dose ITG was safe for hearing and efficient for vertigo attack on resistant MD cases [18].

Gabra et al. compared ITM and ITG treatments. There were 89 patients with MD, 47 of them treated with ITG and 42 of them treated with ITM. Two groups were compared for vertigo attack, tinnitus, aural fullness, PTA, and SDS at 0–6 months and 6–12 months. Both groups had similar vertigo attack number before treatment (P: 0.883). Complete vertigo control was obtained in 82.9% in ITG group and 48.1% in ITM group after 6–12 months of treatment (P: 0.004). Tinnitus and aural fullness control were higher in ITG group than in ITM group (P: 0.002). PTA and SDS values were better in ITM group at pretreatment period ($P < 0.001$). But those values became worse in ITM group at 6–12-month control, and difference disappeared between groups ($P > 0.05$) [3]. According to that study, ITG was more effective than ITM to control MD symptoms [3].

Shea et al. suggested a combination of streptomycin and dexamethasone perfusion for MD. The hearing changes and quality-of-life outcomes of 393 cases of streptomycin/dexamethasone inner ear perfusion were searched retrospectively. All patients underwent one or more 3-day treatments consisting of daily intratympanic injections of a low-dose streptomycin (10 mg/ml)/high-dose dexamethasone (24 mg/ml) mixture plus 16 mg of intravenous dexamethasone. The end point for treatment was adequate control of vertigo. The mean PTA change was 0.89 ± 11 dB and the mean SDS change was 0.49 ± 17 after 3-day treatment. Significant hearing loss was detected in 62 (15.7%) patients and hearing loss was severe

in 20 (5%) of those patients. Ninety percent of the patients had improved quality of life after treatment and 88% of the patients showed improvement in their "vertigo subscore," a domain within the survey that focuses on vertigo control. According to their results, streptomycin/dexamethasone inner ear perfusion is as safe as other aminoglycoside regimens in the hearing of patients with MD and provides good control of vertigo and a significant improvement in quality of life [32].

Sennaroglu et al. compared three methods to control MD symptoms: ITD, ITG, and decompression of the endolymphatic sac (ESD). Dexamethasone was applied to 24 patients and gentamicin was applied to 16 patients by the ventilation tube way. Surgery of ESD was performed in 25 patients. Vertigo control rates of ITD, ITG, and ESD were 72, 75, and 52%, respectively. Total hearing lost was detected in two patients in ITG group. Hearing level decreased in 9 (38%) patients, improved in 4 (16%) patients, and didn't change in 11 (46%) patients in ITD group. They suggested ITD for patients with the vertiginous symptoms still persisting after 6 months of medical treatment. If patients are resistant to this intervention, ITG could be planned for patients with profound sensorineural hearing loss and ESD could be recommended for patients with normal hearing. Vestibular nerve section could be planned as a last chance to control vertigo attacks for patients with good hearing and labyrinthectomy for patients with profound sensorineural hearing loss [33].

Vestibular nervectomy could be planned as a last chance to control vertigo attacks for good hearing.

Quaranta et al. investigated 38 patients with intractable MD with a minimum of 7 years of follow-up. Twenty patients were treated with endolymphatic-mastoid shunt (EMS) surgery and the remaining eighteen patients refused surgery (natural history, NH group). At the last control, 85% of the patients in EMS group and 74% of the NH patients had complete or substantial control of vertigo. The difference between the two groups was not significant. However, it was significant at 2 and 4 years of follow-up. At 2 years, 65% of the EMS patients had complete or substantial control of vertigo and at 4–6 years in 85% of the cases. Only 32% of the NH patients had complete or substantial control of vertigo at 2 years. This percentage had increased to 50% in the fourth year and to 74% in the sixth year. Hearing results in the two groups were not significantly different. Tinnitus disappeared or decreased in 56% of the EMS patients and in 18% of the NH patients. Sixty-seven percent of the EMS patients and twenty-nine percent of the NH patients reported that their aural fullness disappeared. Consequently, vertigo attack reduction was observed earlier in EMS patients than in those who refused surgery [34].

9. Conclusions

Although the fact that definitive treatment of MD has not been found yet, several treatment options are used to control the MD symptoms. Different success rates of symptom relief are given in literature for each option. However, common agreed decision is that ITS can be used in patients with intractable MD to conservative and medical treatment before intratympanic gentamicin and surgical treatments.

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